CLINICAL STUDY PROTOCOL

Protocol Title:	A SINGLE-CENTER, PILOT, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ENSIFENTRINE IN THE RECOVERY OF HOSPITALIZED PATIENTS WITH COVID-19.
Protocol Number:	RPL554-COV-201
Version:	4.0
Amendment Number:	3.0
Investigational Product:	Ensifentrine
Short Title:	Ensifentrine therapy for COVID-19.
Study Phase:	II
Sponsor Name:	Verona Pharma Inc
Legal Registered Address	8045 Arco Corporate Drive | Suite 130 Raleigh, NC 27617
Regulatory Agency Identifying Number(s):	US IND Number: 150701
Date of Protocol:	13 October 2020 (replaces Version 3.0, dated 16 July 2020)

CONFIDENTIAL

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

Kathleen Rickard 13 OCT 2020

Kathleen Rickard, MD **Date**

Chief Medical Officer

Medical Monitor name and contact information can be found in Appendix 2.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1 Document History

Document	Date	Substantial	Region
Amendment 1.0	14-July-2020	Yes	US
Amendment 2.0	16-July-2020	Yes	US
Amendment 3.0	13-October-2020	Yes	US

Amendment 1.0: 14-July-2020

Overall Rationale for Amendment 1.0:

The protocol is amended to revise collection and reporting of AEs to include all AEs and SAEs, not only Grade 3 and 4, and to clarify that worsening of underlying disease that is judged by the investigator to be more severe than expected should be reported as an AE or SAE.

Amendment 2.0: 16-July-2020

Overall Rationale for Amendment 2.0:

The protocol is amended to revise the definition of Adverse Events to include collection of adverse events associated with the underlying disease, not only those judged by the Investigator to be more severe than expected for the patient's condition.

Amendment 3.0: 13-October-2020

Overall Rationale for Amendment 3.0:

The protocol is amended to revise the inclusion criteria to include an anticipated hospital stay of at least 72 hours (following randomization). A stay of 24 or 48 hours is not sufficient time to provide meaningful data due to the limited number of doses of study medication received by the patient.

The Discharge Safety Laboratory Tests will be changed from a requirement to at the discretion of the treating physician, and if performed, may be completed within 24 hours of discharge. This is a real-life study, therefore, additional lab tests at or prior to discharge may not be medically necessary according to the patient's treating physician.

Table 2 Description of Changes in the Amendment

Amendment 1.0		
Section # and Name	**Description of Change**	**Brief Rationale**
Table numbering	Table numbers all shifted by 2 to accommodate 2 Tables added for the Amendment information.	Administrative change to accommodate Amendment Section.
Section 8.6, Adverse Events Section 8.6.1, time period and frequency for collecting AE and SAE information	The following statement was deleted: "Given the nature of severity of the underlying illness, subjects will have many symptoms and abnormalities in vital signs and laboratory values. All Grade 3 and 4 AEs will be captured as AEs in this trial." Text was modified to clarify that collection of AE information would include all AEs and SAEs, not only grade 3 and 4.	Substantial change to collect information on all AEs and SAEs, not just Grades 3 and 4.
Section 8.6.7, Disease-related events and/or disease related outcomes not qualifying as AEs or SAEs	This section including the following language was deleted. "Clinical worsening of COVID-19 symptoms is an expected disease-related outcome and should be captured as part of the daily assessments."	
Section 10.5, Safety	The sentence "Safety endpoints include SAEs and Grade 3 and 4 AEs" was revised to "Safety endpoints include SAEs and AEs"	Substantial change to report summary data on all AEs and SAEs, not just grades 3 and 4.
Appendix 4, Definition of AE	The 4th bullet was deleted: "Given the nature of severity of the underlying illness, subjects will have many symptoms and abnormalities in vitals and laboratory. All Grade 3 and 4 AEs	Substantial change to collect information on all AEs and SAEs, not just Grades 3 and 4,

Events Meeting the AE Definition	will be captured as AEs in this trial." The 7th bullet was deleted due to redundancy and clarification: "The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes and AE or SAE."	and to clarify a redundant bullet.
Section 6.3.1, Study Medication Dispensing	Language referring to "kit medication ID number" and "kit lists" was removed.	Administrative change for clarification.
Amendment 2.0		
Section # and Name	**Description of Change**	**Brief Rationale**
Appendix 4, Events meeting the definition of an AE	Bullet 1: the following text was deleted "(ie, not related to progression of underlying disease)." Bullet 3: the following language was added "or those associated with underlying disease including expected progression, signs, or symptoms of the disease/disorder being studied."	Substantial change to collect AEs associated with underlying disease.
Events NOT meeting the definition of an AE	Bullet 1: the following language was deleted "Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be	

Definition of SAE	more severe than expected for the patient's condition." Bullet 2: the following language was deleted "or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition." This section states "If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met." The following example was deleted "(e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease)."	
Amendment 3.0		
Section # and Name	**Description of Change**	**Brief Rationale**
1.3 Schedule of Activities	In Study Treatment Period column for Safety Laboratory Tests, clarified with the symbol **β** and added this statement in the notes section of the table "**Discharge safety laboratory tests may be completed at the discretion of the treating physician and, if completed, may be completed within 24 hours of the patient's discharge from the hospital.**"	The treating physician may not deem it necessary to have additional hematology or blood chemistry tests ordered prior to discharge
Section 5.1 Inclusion Criteria # 4	Clarified inclusion criteria #4 to read as follows: **Patient with a** clinical status consistent with 3, 4 or 5 on the Ordinal scale **and for whom the anticipated hospitalization is at least 72 hours (after randomization)**.	Patients with 24-48 hours in the hospital are unlikely to provide enough data due to the small number of doses of study medication.
Section 10.5 Safety	Added the term "**Available**" at the start of the second paragraph.	Not all patients will have discharge safety laboratory

		values since these may now be performed at the discretion of the treating physician.
Appendix 3. Laboratory Tests	Added the language in bold to the second paragraph. "The following safety laboratory tests are required for eligibility verification and upon discharge **at the discretion of the treating physician and, if completed, may be completed within 24 hours of the patient's discharge from the hospital** if not already conducted as part of standard of care:"	The Investigator and the Treating Physician are not the same. This is a real-life study and, as such, the treating physician may not deem it necessary to have additional hematology or blood chemistry tests ordered prior to discharge.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A single-center, pilot randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ensifentrine in the recovery of hospitalized patients with COVID-19.

Short Title:

Ensifentrine therapy for COVID-19.

Rationale

Verona Pharma is developing inhaled nebulized ensifentrine for the maintenance treatment of Chronic Obstructive Pulmonary Disease (COPD).

Ensifentrine is a dual inhibitor of Phosphodiesterase 3 (PDE3) and PDE4 which has demonstrated both bronchodilator and anti-inflammatory effects in clinical studies (Singh, 2018; Singh, 2020; Franciosi, 2013). Ensifentrine has been studied in patients with COPD as a nebulized suspension, dry powder inhaler (DPI) and pressurized metered dose inhaler (pMDI). Overall, ensifentrine was well tolerated in 17 clinical studies conducted to date, with adverse event incidence and severity generally similar to those in the placebo-treated group. Verona Pharma is entering Phase III clinical development with nebulized suspension ensifentrine as a maintenance therapy for patients with COPD.

It is postulated that inhaled ensifentrine treatment in patients with COVID-19 will effectively bronchodilate patients, reducing symptoms of dyspnea and improve the patient's oxygen levels thus reducing the need for supplemental oxygen. Activity of ensifentrine related to reduction of viral-induced inflammation and CFTR stimulation may help patients clear the virus more rapidly and help prevent further clinical deterioration resulting from reduced oxygenation and secondary infections related to mucus hypersecretion. As such, the goal of ensifentrine treatment in patients with COVID-19 is to improve clinical status, facilitate recovery and prevent the progression of the disease leading to mechanical ventilation by allowing the patient to breath better during the infection, to reduce the inflammation in the lung and facilitate patient recovery from COVID-19.

Objectives and Endpoints

Primary

The primary objective is to evaluate the effect of ensifentrine on the proportion of patients with recovery from COVID-19 over 29 days.

The primary endpoint is to evaluate the effect of ensifentrine on the proportion of patients with recovery (Day 29).

- Day of recovery is defined as the first day on which subjects satisfies one of the following two categories from the 7-point ordinal scale:
    - not hospitalized, no limitations of activities;
    - not hospitalized, limitation of activities, home oxygen requirement, or both.

Secondary

Secondary objectives include the evaluation of:

- the effect of ensifentrine on COVID-19 related time to recovery, clinical status and risk of deterioration and
- the effect of ensifentrine on hospitalization, non-invasive and invasive ventilation and oxygen use.

Secondary endpoints include:

- Time to recovery defined as satisfying one of the following two categories from the 7-point ordinal scale (Day 1-Day 29):
    - not hospitalized, no limitations of activities;
    - not hospitalized, limitation of activities, home oxygen requirement, or both.
- Proportion of patients with recovery at day 60.
- Proportion of patients with improvement (from Day 1) of one category using the 7-point ordinal scale (Days 7, 14 and 29).
- Proportion of patients with improvement of two categories using the 7-point ordinal scale (Days 7, 14 and 29).
- All-cause mortality at Days 29 and 60.
- Proportion of patients alive and not in respiratory failure (invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) at Day 29.
- Proportion of patients needing re-hospitalization over 60 days.
- Duration of hospitalization from Day 1 (Day 1 - Day 29; measured in days).
- Mean change from baseline in 7-point ordinal scale (Days 7, 14 and 29).
- Total time on supplemental oxygen (Day 1 - Day 29; measured in days).
- Incidence and duration of new non-invasive ventilation or high flow oxygen use (Day 1 - Day 29; measured in days).
- Incidence and duration of new oxygen use (Day 1 - Day 29; measured in days).
- Incidence and duration of new mechanical ventilator use (Day 1 - Day 29; measured in days).
- Proportion of patients receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at Days 7, 14 and 29 (7-point ordinal scale criteria #6).

Safety

Safety objectives include the evaluation of the safety and tolerability of ensifentrine in patients with COVID-19.

Safety endpoints include:

- The incidence of adverse events (AEs)
- Vital signs.

Overall Design

The purpose of this study is to evaluate the effect of ensifentrine in patients hospitalized with COVID-19 infection in terms of the proportion of patients in recovery from COVID-19 at Day 29.

This is a single center, randomized, double-blind, parallel group, placebo-controlled study to determine the efficacy and safety of ensifentrine 2 mg twice daily (BID) administered via pressurized metered dose inhaler (pMDI) added on to standard of care (SoC) treatment for COVID-19 infection compared to subjects receiving SoC plus placebo.

Patients 18 to 80 years of age must be hospitalized with a confirmed diagnosis of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test and displays at least one of the following: Respiratory rate greater than 24, new cough, new atypical chest pain, new dyspnea, oxygen saturation <97% at rest, chest x-ray with new changes consistent with COVID-related airspace disease.

Patients meeting criteria for inclusion and none of the criteria for exclusion at randomization will be randomized to receive study medication in the study until hospital discharge or up to 29 days of treatment, whichever comes first. Patients will be randomized 2:1 to receive one of the following study treatments:

- Treatment Arm 1 (n=30): Blinded ensifentrine (2 mg) pMDI BID + Standard of Care treatment for COVID-19 infection
- Treatment Arm 2 (n=15): Blinded placebo pMDI BID + Standard of Care treatment for COVID-19 infection

Randomized patients will receive blinded ensifentrine or placebo twice daily, approximately 12 hours apart in the morning and evening, through 29 days or until discharge from hospital, whichever is first. Patients will self-administer 4 actuations (puffs) pMDI observed by study staff at each dosing event.

During the treatment period, patients will undergo all assessments and procedures as outlined in the Schedule of Activities (SoA) until hospital discharge. Patients completing treatment will complete a study contact (telephone or visit as required) within 4 to 10 days of discharge or early withdrawal. All enrolled patients will complete a telephone contact 26 to 32 days and 55-65 days following receipt of 1st dose of study medication for assessment of clinical status via the ordinal scale, need for re-hospitalization and vital status.

The study design is displayed in Figure 1 and the SoA is in Table 3.

Number of Investigators and Study Centers

This is a single-site study conducted at the University of Alabama at Birmingham Hospital (UAB). The principle investigator is Dr. J. Michael Wells, Division of Pulmonary, Allergy, and Critical Care Medicine.

Number of Patients

Approximately 45 randomized patients are planned.

Treatment Groups and Duration

Every patient enrolled will receive UAB's SoC treatment for COVID-19 infection.

Upon enrollment, patients will be randomized 2:1 to receive blinded ensifentrine via pMDI BID + SoC or placebo pMDI BID + SoC over 29 days or until discharge from hospital, whichever is first.

- Treatment Arm 1 (n=30): Blinded ensifentrine (2 mg) pMDI BID + Standard of Care treatment for COVID-19 infection
- Treatment Arm 2 (n=15): Blinded placebo pMDI BID + Standard of Care treatment for COVID-19 infection

Statistical Methods

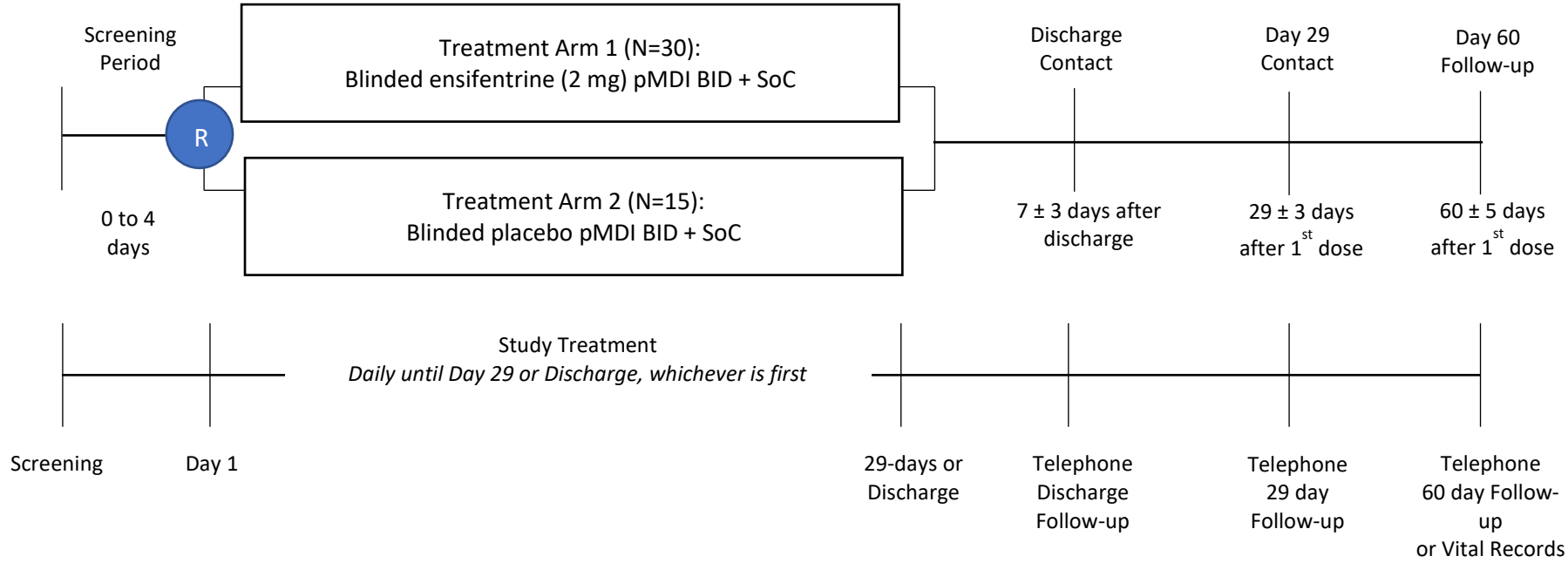
All analyses are considered exploratory and hypothesis-generating.

Sample Size

This is a pilot study and it is not formally powered based on any specific endpoint. Sample size has been set to minimize the number of patients exposed, but still large enough to give reliable estimates on the efficacy and safety of ensifentrine in the target population.

1.2 Schema

Figure 1. Study schematic.



Abbreviations - BID: twice daily; SoC: standard of care treatment for COVID-19 infection; mg: milligrams; n: number of patients; pMDI: pressurized metered dose inhaler; R: randomization.

1.3 Schedule of Activities

Table 3. Schedule of activities.

	Procedures for Patients Completing the Study						Procedures for Early Termination or Withdrawal			
Tests and Procedures	**Screening / Baseline**	**Day 1[†]**	**Study Treatment Period (Days 2 – 29)**	**Discharge contact[‡]**	**Day 29 contact[‡‡]**	**Day 60 Follow-up[‡‡‡]**	**Early Termination / Withdrawal**	**Discharge contact[‡]**	**Day 29 contact[‡‡]**	**Day 60 Follow-up[‡‡‡]**
	0 to 4 days before Day 1	*(Visit 1) all pre-dose*	*Daily until hospital discharge or Day 29, whichever is first (or as noted)*	*(7 ± 3 days)*	*(29 ± 3 days)*	*(60 ± 5 days)*		*(7 ± 3 days)*	*(29 ± 3 days)*	*(60 ± 5 days)*
Written Informed Consent	X									
Demographics	X									
Record medical history and hospital admission data	X									
Brief physical exam*	X									
Safety laboratory tests hematology, chemistry (non-fasting), urinalysis, serology, pregnancy test (as applicable)[Ω]	X		At discharge or on Day 29[β]				X			
Review Inclusion/Exclusion criteria and categorize disease severity	X									
Randomization		X								
Vital signs including oxygen saturation[¥]	X	X	X[1]				X[1]			
7-point ordinal scale assessment[β]	X	X	X[1]	X	X	X	X[1]	X	X	X
Record SoC concomitant medication and treatments	X	X	X				X			
Record SoC laboratory test results (e.g., hematology, chemistry, serology, pathology, radiology, urinalysis, etc.)^	X	X	X				X			
Adverse Events assessment	X	X	X	X	X	X	X	X	X	X
Dispense blinded study medication and record		X	On Days 12 and 24							
Collect used, blinded study medication and record			On Days 12, 24 and 29 (or discharge)				X			
Study medication training and observation and record		X								

Tests and Procedures	Procedures for Patients Completing the Study						Procedures for Early Termination or Withdrawal			
	Screening / Baseline	**Day 1†**	**Study Treatment Period (Days 2 – 29)**	**Discharge contact‡**	**Day 29 contact‡‡**	**Day 60 Follow-up‡‡‡**	**Early Termination / Withdrawal**	**Discharge contact‡**	**Day 29 contact‡‡**	**Day 60 Follow-up‡‡‡**
	0 to 4 days before Day 1	*(Visit 1) all pre-dose*	*Daily until hospital discharge or Day 29, whichever is first (or as noted)*	*(7 ± 3 days)*	*(29 ± 3 days)*	*(60 ± 5 days)*		*(7 ± 3 days)*	*(29 ± 3 days)*	*(60 ± 5 days)*
Dose blinded study medication with study staff and record[Σ]		X	twice daily (morning and evening) until discharge or Day 29[2]				X[2]			
Follow-up vital status				X	X	X		X	X	X
Re-hospitalization/Still in hospital status				X	X	X		X	X	X
Vital records search, if needed						X				X

†	Day 1 may take place on the same day as the screening/baseline visit, if appropriate. If Day 1 activities take place on the same day as screening/baseline visit, only 1 ordinal scale assessment and vital sign assessment are necessary, but they must be completed prior to dosing.
‡	Discharge Contact: contact with the patient will take place 4 to 10 days after discharge from hospital within the 29-day treatment period. If the patient remains hospitalized after Day 29, contact with the patient will take place 4 to 10 days after receipt of last dose of study medication on Day 29.
‡‡	Day 29 Contact (if patient discharged prior to Day 29): contact with the patient will take place 26 to 32 days after first dose of study medication. If the Discharge Contact and Day 29 Contact fall within same window, this contact will be combined as the Day 29 Contact.
‡‡‡	Day 60 Follow-up: contact with the patient will take place 55 to 65 days after first dose of study medication.
*	Record the physical exam documented by the treating team on the day of screening, and verify key parts (heart, lung).
Ω	If kidney (creatinine), liver (alanine aminotransferase or aspartate aminotransferase) and pregnancy (if applicable, via serum) were not run prior, they are required during the screening process. Refer to exclusion criteria in Section 5.2 and Appendix 3.
β	Discharge safety laboratory tests may be completed at the discretion of the treating physician and, if completed, may be completed within 24 hours of the patient's discharge from the hospital.
¥	Vital signs should be recorded each morning at approximately the same time of a given study day. Variables: Respiration rate (per minute), Oxygen saturation (SpO2), Any supplemental oxygen (yes/no), Body temperature, Systolic blood pressure, Heart rate (pulse rate per minute); and Level of consciousness graded on the AVPU scale (Alert, Verbal = voice response present, Pain = pain response present, Unresponsive). Refer to Section 8.1.3.
1	These assessments are not required to be completed prior to morning blinded study medication dosing.
β	Ordinal scale clinical improvement assessed and recorded each morning at approximately the same time. The categories are as follows: 1=not hospitalized, no limitations of activities; 2=not hospitalized, limitation of activities, home oxygen requirement, or both; 3=hospitalized, not requiring supplemental oxygen but requiring ongoing medical care; 4=hospitalized, requiring any supplemental oxygen; 5=hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices; 6=hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 7=death. Refer to Section 8.1.1.
^	Laboratory results performed as recommended by UAB treating physician: Record daily (or as performed) WBC, neutrophil count, lymphocyte count, creatinine values. Record every 2-3 days (or as performed) a) Inflammatory markers and b) LFTs. Those recommended for UAB staff include: BMP, CBC w/ diff, LFT, IL-6, ferritin, D-dimer every three days. See Section 8.1.4 and Appendix 3.
Σ	Study staff, nursing and/or respiratory therapy to administer. The person administering and observing cannot be the unblinded pharmacist.
2	Blinded study medication may be dosed as deemed appropriate by Investigator on day of discharge.

2 INTRODUCTION

2.1 Study Rationale

According to the US Centers for Disease Control and Prevention, most patients with COVID-19 will experience signs and symptoms including fever, cough, shortness of breath, and sputum production. Most patients (81%) have what is considered mild to moderate illness (mild symptoms up to mild pneumonia), with approximately 14% experiencing severe effects (dyspnea, hypoxia, or >50% lung involvement from pneumonia on imaging). Clinical goals for patients hospitalized with COVID-19 include preventing clinical deterioration (including progression to mechanical ventilation), improving dyspnea and reducing hypoxia, and clearing the infection from the lungs. An intervention that could improve clinical status and facilitate recovery while minimizing progression to mechanical ventilation in patients hospitalized with COVID-19 is urgently needed.

Bronchodilators have been used extensively in COVID-19 patients to alleviate respiratory symptoms leading to an albuterol (salbutamol) metered dose inhaler (MDI) shortage. In addition to experimental anti-viral therapies, anti-inflammatory agents such as IL-6, monoclonal antibodies are also under evaluation for the treatment of patients with COVID-19. It was recently reported that elevated inflammatory cells and markers such as TNFα and IL-6 have been shown to be associated with COVID-19 severity in patients, indicating an inflammatory hyper-response akin to a cytokine storm that is associated with poor outcomes (Gong, 2020). As such, agents that target these inflammatory mediators, such as inhibitors of phosphodiesterase (PDE) 3 and PDE4, are potential therapeutic interventions of significant interest.

The purpose of this study is to evaluate the efficacy and safety of, ensifentrine (RPL554), in combination with SoC treatment for COVID-19 infection for hospitalized patients.

2.2 Ensifentrine Background

PDEs are enzymes that impact a range of cellular functions within the airways and the lungs by modulating levels of cyclic nucleotides. PDEs 3 and 4 are known to play key roles in important cellular function related to airways disease, such as smooth muscle relaxation, mucus production, ciliary beat frequency, airway re-modeling and inflammatory mediator release (Zuo, 2019; Boswell-Smith, 2006; Abbott-Banner, 2014; Matera, 2014). Thus, selective PDE inhibition, specifically PDE3 and PDE4, may be useful in the treatment of respiratory disease.

Ensifentrine is an investigational, inhaled, dual inhibitor of PDE3 and PDE4 which has demonstrated both bronchodilator and anti-inflammatory effects in clinical studies in healthy individuals as well as those with asthma, allergic rhinitis and COPD (Singh, 2018; Singh, 2020; Franciosi, 2013). Ensifentrine has been studied in patients with COPD as a nebulized suspension therapy, DPI and pMDI. Overall, ensifentrine was well tolerated in 17 clinical studies conducted to date, with adverse event incidence and severity generally similar to those in the placebo-treated group. Verona Pharma is entering Phase III clinical development with nebulized ensifentrine as a maintenance therapy for patients with COPD.

It is postulated that ensifentrine treatment in patients with COVID-19 will effectively bronchodilate patients, reducing symptoms of dyspnea and improve the patient's oxygen

levels thus reducing the need for supplemental oxygen. Activity of ensifentrine related to reduction of viral-induced inflammation and CFTR stimulation may help patients clear the virus more rapidly and help prevent further clinical deterioration resulting from reduced oxygenation and secondary infections related to mucus hypersecretion. As such, the goal of ensifentrine treatment in patients with COVID-19 is to improve clinical status, facilitate recovery and prevent the progression of the disease leading to mechanical ventilation by allowing the patient the patient to breath better during the infection, to reduce the inflammation in the lung and facilitate patient recovery from COVID-19.

The safety, bronchodilator, bronchoprotective and anti-inflammatory activities of ensifentrine have been evaluated in 17 clinical trials involving more than 1300 subjects. In the clinical studies performed to date, nebulized ensifentrine has demonstrated pronounced bronchodilator effects in healthy subjects and in patients with COPD or asthma. Nebulized ensifentrine has demonstrated bronchodilator and anti-inflammatory effects in proof of concept studies in healthy patients, and those with asthma or COPD (Franciosi, 2013; Singh, 2018; Singh, 2020; Bjermer, 2019). Additionally, anti-inflammatory effects have been observed in a model of COPD-like inflammation in healthy subjects (Franciosi, 2013). A Phase II single and repeat dose study with ensifentrine in a dry powder inhaler (DPI) format up to 3 mg in 37 patients with COPD showed that single and repeat doses of twice daily ensifentrine over one week had a rapid, dose-dependent, and statistically significant bronchodilatory effect up level over 12 hours.

A new formulation was developed to allow for delivery of ensifentrine using a convenient, hand-held pMDI. In Part A of a two-part Phase 2 study, ensifentrine delivered via pMDI was evaluated as a single dose in patients with COPD. Part B of this study is on hold pending resolution of COVID-related impacts on patients and sites. The active pharmaceutical ingredient used in the pMDI formulation is the identical physical form and morphology as that used in the nebulizer suspension product in previous studies. Furthermore, a non-clinical assessment of local and systemic toxic potential of a dry powder inhaler (DPI) formulation of ensifentrine (of the identical physical form and morphology) blended with lactose was conducted in a 2-week inhalation study in Han Wistar rats. The purpose of this non-clinical study was to support single and repeat dose clinical studies with both a DPI as well as a pMDI formulation, consisting of ensifentrine suspended in hydrofluoroalkane (HFA)-134a propellant only. Results from this initial bridging toxicology study with an ensifentrine lactose dry powder blend showed no new findings when this vehicle formulation is used at similar exposure levels, and this body of data supports clinical evaluation of both the DPI and pMDI formulations. Finally, single dose pharmacokinetic data from the ensifentrine pMDI in patients with COPD dosed from 0.1 mg to 3 mg was analogous to that observed following a single dose with ensifentrine DPI in COPD patients regarding both Cmax and $AUC_{0\text{-}12h}$.

Overall, ensifentrine was well tolerated in all clinical studies completed to date, with adverse event (AE) incidence and severity generally similar to those in the placebo-treated group. Serious adverse events (SAEs) have been uncommon and there is no apparent pattern in the SAEs reported to date.

Information on the background of ensifentrine as described in this section can be found in the Verona Pharma plc. Ensifentrine Clinical Investigators Brochure v. 19, 20th May 2020, unless otherwise cited.

2.3 Benefit/Risk Assessment

No significant medical risks to patients have been identified from studies conducted to date with ensifentrine administered in the nebulized, dry powder or metered dose inhalation formulations. With all formulations of inhaled ensifentrine studied to date (17 studies, n > 1300 patients), including nebulized suspension (15), DPI (1) and pMDI (1), including 2 x 4-week, 400-patient studies with nebulized ensifentrine in COPD patients up to twice daily doses of 6 mg, ensifentrine has been well tolerated to date, with adverse event (AE) incidence and severity generally similar to those in the placebo-treated group. In studies with COPD patients, this included patients with many underlying co-morbidities including cardiovascular disease, diabetes, hypertension and underlying renal dysfunction. Adverse events related to cardiovascular or gastrointestinal systems have not been associated with ensifentrine treatment. Serious adverse events (SAEs) have been uncommon and there is no apparent pattern in the SAEs reported to date. The risk of drug-drug interactions with ensifentrine is very low.

A small, transient increase in peak heart rate (HR) of 3 bpm was observed with the 6 mg nebulized dose after 4 weeks of twice daily treatment in patients with COPD, an increase in peak pulse rate (but not HR) of 6 bpm was observed with the 3 mg dose after 7 days of twice daily DPI treatment in patients with COPD, and an increase in peak heart rate was observed with the 3 mg and 6 mg single dose of pMDI of 7 beats per minute (bpm) and 11 bpm, respectively, in patients with COPD, but no corresponding increase in pulse rate was observed for the 3 mg dose. In healthy volunteers, a single dose of 6 mg nebulized ensifentrine showed an increase in peak HR of 12 bpm at supratherapeutic exposures. These small, transient increases in peak heart rate are not considered clinically meaningful and have not been associated with adverse clinical outcomes.

Ensifentrine has been demonstrated to have favorable non-clinical toxicology and PK profiles when delivered via the inhaled route as both a nebulized suspension and as a DPI. Following single dosing, the PK profiles from ensifentrine DPI and MDI are similar in patients with COPD.

Effects on reproductive performance in male rats given the highest dose of 15.5 mg/kg/day included lower number of pairings of dosed males resulting in pregnancy in undosed females, higher pre and post implantation loss resulting in lower mean litter size, and lower sperm motility and higher abnormal sperm. No ensifentrine-related adverse effects were observed at 5.75 mg/kg/day (20.5 times the maximum recommended human dose based on AUC). There were no effects on embryo-fetal survival and development in either rats or rabbits in the main embryo-fetal development studies. The effects of ensifentrine on fertility and reproductive performance in female rats have not yet been assessed.

Ensifentrine has statistically and clinically significant bronchodilator as well as anti-inflammatory effects. As such, the clinical development of ensifentrine is focused on the treatment of obstructive and inflammatory lung diseases, including COPD. Considering the consistent improvements in lung function, symptoms and health-related quality of life across multiple studies in patients with COPD and the overall favorable safety profile in studies to date, the benefit/risk profile of ensifentrine in patients with COVID-19 is considered positive.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ensifentrine can be found in the Verona Pharma plc. Ensifentrine Clinical Investigators Brochure v. 19, 20th May 2020.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary objective

The primary objective is to evaluate the effect of ensifentrine on the proportion of patients with recovery from COVID-19 over 29 days.

3.1.2 Secondary objectives

- To evaluate the effect of ensifentrine on COVID-19 related time to recovery, clinical status and risk of deterioration,
- To evaluate the effect of ensifentrine on hospitalization, non-invasive and invasive ventilation and oxygen use.

3.1.3 Safety objective

- To evaluate the safety and tolerability of ensifentrine in patients with COVID-19.

3.2 Endpoints

3.2.1 Primary endpoint

The primary endpoint is to evaluate the effect of ensifentrine on the proportion of patients with recovery (Day 29).

- Day of recovery is defined as the first day on which subjects satisfies one of the following two categories from the 7-point ordinal scale:
    - not hospitalized, no limitations of activities;
    - not hospitalized, limitation of activities, home oxygen requirement, or both.

3.2.2 Secondary endpoints

- Time to recovery defined as satisfying one of the following two categories from the 7-point ordinal scale (Day 1-Day 29):
    - not hospitalized, no limitations of activities;
    - not hospitalized, limitation of activities, home oxygen requirement, or both.
- Proportion of patients with recovery at Days 7, 14, 29 and 60.
- Proportion of patients with improvement (from Day 1) of one category using the 7-point ordinal scale at Days 7, 14 and 29.
- Proportion of patients with improvement (from Day 1) of two categories using the 7-point ordinal scale at Days 7, 14 and 29.
- All-cause mortality at Days 29 and 60.
- Proportion of patients alive and not in with respiratory failure (invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) at Day 29.
- Proportion of patients needing re-hospitalization over 60 days.
- Duration of hospitalization from Day 1 (Day 1 - Day 29; measured in days).

- Mean change from baseline in 7-point ordinal scale (Days 7, 14 and 29).
- Total time on supplemental oxygen (Day 1 - Day 29; measured in days).
- Incidence and duration of new non-invasive ventilation or high flow oxygen use (Day 1 - Day 29; measured in days).
- Incidence and duration of new oxygen use (Day 1 - Day 29; measured in days).
- Incidence and duration of new mechanical ventilator use (Day 1 - Day 29; measured in days).
- Proportion of patients receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at Days 7, 14 and 29 (7-point ordinal scale criteria #6).

3.2.3 Safety Endpoints

- Incidence of Adverse Events (AEs)
- Vital Signs

4 STUDY DESIGN

4.1 Overall Design

The purpose of this study is to evaluate the effect of ensifentrine on the proportion of patients hospitalized with COVID-19 infection with recovery over 29 days.

This is a single center, randomized, double-blind, parallel group, placebo-controlled study to determine the efficacy and safety of ensifentrine 2 mg BID administered via pMDI added on to SoC treatment for COVID-19 infection compared to subjects receiving SoC plus placebo.

Patients 18 to 80 years of age must be hospitalized with a confirmed diagnosis of SARS-CoV-2 infection confirmed by PCR test and displays at least one of the following: Respiratory rate greater than 24, new cough, new atypical chest pain, new dyspnea, oxygen saturation <97% at rest, chest x-ray with new changes consistent with COVID-19 related airspace disease.

Patients meeting criteria for inclusion and none of the criteria for exclusion at randomization will be randomized to receive study medication until to hospital discharge or up to 29 days of treatment, whichever comes first. Patients will be randomized 2:1 to receive one of the following study treatments:

- Treatment Arm 1 (n=30): Blinded ensifentrine (2 mg) pMDI BID + Standard of Care treatment for COVID-19 infection
- Treatment Arm 2 (n=15): Blinded placebo pMDI BID + Standard of Care treatment for COVID-19 infection

Randomized patients will receive blinded ensifentrine or placebo twice daily, approximately 12 hours apart in the morning and evening, through 29 days or until discharge from hospital, whichever is first. Patients will self-administer 4 actuations (puffs) pMDI observed by study staff at each dosing event.

During the treatment period, patients will undergo all assessments and procedures as outlined in the SoA until hospital discharge. Patients completing treatment will complete a study contact (telephone or visit as required) within 4 to 10 days of discharge or early withdrawal. All enrolled patients will complete a telephone contact 26 to 32 days and 55-65 days following receipt of 1st dose of study medication for assessment of clinical status via the ordinal scale, need for re-hospitalization and vital status.

4.2 Scientific Rationale for Study Design

Inhaled ensifentrine has three main pillars of pharmacology relevant to treatment of patients with COVID-19: 1) bronchodilation 2) anti-inflammatory effects and 3) CFTR stimulation.

1) Bronchodilation: In patients experiencing acute symptoms of shortness of breath and cough, acute treatment with ensifentrine can be used to improve oxygenation, alleviate symptoms, improve shortness of breath and reduce the work of breathing. Ensifentrine could be used as monotherapy or added on to short acting or long-acting beta2-agonists or muscarinic antagonists (SABA, LABA, SAMA, LAMA or SABA/SAMA, LABA/LAMA combinations) providing immediate bronchodilation (≤ 5 minutes) to patients who are

having trouble breathing and/or with excessive cough. Clinical effects of ensifentrine on lung function are described in detail in the Investigator Brochure.

2) Anti-Inflammatory effects: It is expected that ensifentrine will help clear the virus-induced lung inflammation via reduction in local inflammatory cell numbers such as neutrophils, eosinophils, lymphocytes, macrophages and pro-inflammatory mediators such as TNFα and IL-6.

Inhaled ensifentrine has demonstrated anti-inflammatory effects in a model of COPD-like inflammation in healthy subjects. In healthy subjects dosed with a nebulized solution of ensifentrine (0.018 mg/kg, approximately 1 mg dose) once daily for 6 days, induced sputum 6 hours after a lipopolysaccharide challenge showed a reduction in absolute numbers of neutrophils ($p = 0.002$), macrophages ($p = 0.044$), eosinophils ($p = 0.001$), lymphocytes ($p = 0.001$) and total cells ($p = 0.002$) (Franciosi, 2013).

In vitro, ensifentrine has demonstrated functional inhibition of PDE4 via inhibition of TNFα production in LPS-stimulated human monocytes (520 nM) and inhibition of proliferation of human mononuclear cells stimulated with PHA (460 nM) (Boswell-Smith, 2006) Additional work in animal models has shown that ensifentrine reduces inflammatory cell recruitment (eosinophil) following antigen challenge in guinea pigs.

Other inhibitors of PDE4 have shown additional anti-inflammatory effects in assays where ensifentrine has not yet been tested, although it is expected that the pharmacology should be analogous or enhanced through inhibition of both PDE3 and PDE4: the PDE4 inhibitor CHF-6001 reduced IL-6 in vitro in dendritic cells (Gianello, 2019) and roflumilast reduced IL-6 in bronchoalveolar lavage fluid in COPD patients (Savelikhina, 2018). Furthermore, these inhibitors of PDE4, CHF-6001 and roflumilast have also been shown in vitro to reduce in viral-induced inflammation in human bronchial epithelial (HBE) cells infected with rhinovirus (RV) and respiratory syncytial virus (RSV), respectively (Edwards, 2016; Mata, 2013). Roflumilast has also shown that the PDE4 inhibitory mechanism may reduce viral load as shown with roflumilast in HBE infected with RSV over 10 days (Mata, 2013). It should be noted that selective inhibitors of PDE4 such as roflumilast and CHF-6001 do not have bronchodilatory activity, and use of roflumilast, an oral inhibitor of PDE4, is limited by significant gastrointestinal effects. Ensifentrine is delivered via the inhalation route and gastrointestinal effects observed with other PDE4 inhibitors have not been observed in ensifentrine studies.

3) CFTR Stimulation: Ensifentrine may also facilitate mucociliary clearance in patients via stimulation of CFTR, often found to be downregulated or functionally impaired in patients with pneumonia. In vitro evaluation of ensifentrine in human bronchial epithelial cells demonstrated that ensifentrine stimulates CFTR-dependent ion secretion across bronchial epithelial cells isolated from patients carrying the R117H/F508del cystic fibrosis genotype (Turner, 2016). Ensifentrine also significantly increased ciliary beat frequency in primary human bronchial epithelial cells at a similar magnitude to what was observed with PDE4 control, roflumilast.

4.2.1 Rationale for ensifentrine in treatment of COVID-19

In terms of clinical outcomes, Verona Pharma hypothesizes that ensifentrine treatment of patients with COVID-19 will effectively result in bronchodilation in patients, reducing symptoms of dyspnea and improve the patient's oxygen levels thus reducing the need for supplemental oxygen. Activity of ensifentrine related to reduction of viral-induced inflammation and CFTR stimulation may facilitate viral clearance more rapidly and help

prevent further clinical deterioration resulting from reduced oxygenation and secondary infections related to mucus hypersecretion. As such, the goal of ensifentrine treatment in patients with COVID-19 is to improve clinical status, facilitate recovery and prevent the progression of the disease leading to mechanical ventilation by allowing the patient to breathe better during the infection, to reduce the inflammation in the lung and facilitate patient recovery from COVID-19 infection.

Because ensifentrine provides bronchodilation via its inhibition of PDE3 and PDE4, anti-inflammatory effects following inhaled administration including the potential to decreased viral-induced inflammation, and bronchial cell CFTR stimulation, this pharmacologic therapy, delivered via pMDI, may serve as an innovative treatment for patients with COVID-19.

This study will expand our knowledge and understanding about how ensifentrine can be used to facilitate recovery or prevent deterioration in hospitalized, COVID-19 patients.

4.3 Justification for Design

This study is designed as a randomized, double-blind parallel group study evaluating impactful outcomes to patients, treating physicians, and healthcare facilities. As a small, unpowered pilot study, Verona Pharma aims to quickly collect data informing on the potential utility of inhaled ensifentrine pMDI in patients with COVID-19 by evaluation of trends across key independent endpoints.

The study is randomized 2:1 to ensifentrine:placebo in order to minimize the number of patients exposed to placebo during the study. A treatment duration of up to 29 days was selected to ensure that most hospitalized patients could receive study treatment during their full course of hospitalization, as the CDC has recently reported the median duration of hospitalization in patients who survived to be 10 to 13 days and median range of viral shedding among hospitalized patients to be 12–20 days (CDC Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19), June 2, 2020).

The patient population includes hospitalized patients with moderate to severe COVID-19, as we anticipate ensifentrine benefit including preventing progression to respiratory failure or other clinical conditions defined as Critical COVID-19 (FDA COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry).

Ensifentrine has not shown evidence of liver injury in trials including over 1300 patients. Nonclinical data indicate that circulating ensifentrine is rapidly and extensively metabolized. At physiologically relevant concentrations (approximately 3 nM), metabolism is primarily mediated by cytochrome P-450 (CYP) 2C9 (93%); and to a lesser extent CYP2D6 (24%) and CYP3A4 (less than 5%). A drug-drug interaction study in healthy volunteers has shown that concomitant dosing of nebulized ensifentrine 3 mg with steady state fluconazole, an inhibitor of CYP2C9 and CYP3A4, resulted in an increase in Cmax and AUC0-inf of 41% and 63% when compared with ensifentrine alone (RPL554-PK-102; IBv19). This less than 2-fold increase is not considered clinically meaningful, as ensifentrine of up to 6 mg twice daily was found to be well tolerated with a comparable adverse event profile to placebo for over 4 weeks of dosing (Study RPL554-CO-203, IBv19). Because of this data, patients with some level of liver enzyme

elevation may be recruited into the study as it is not expected to have a meaningful impact on exposures (UAB is reporting that approximately 8% of patients hospitalized with COVID-19 have ALT >2x ULN and approximately 19% have AST >2x ULN). Analysis of urine samples in clinical study RPL554-PK-102 showed that after a 3 mg nebulized dose, urinary elimination of unchanged ensifentrine was negligible (<0.3% of the dose from RPL554-PK-102; IBv19). An analysis of trough plasma concentrations, Cmax and AUC0-12h in 127 patients enrolled in Phase 2 studies with mild and moderate renal impairment (GFR 30 to 90 mL/min) compared with patients with normal renal function (GFR ≥90 mL/min) did not show evidence of increased exposures in patients with reduced renal function. Patients with significant hepatic impairment/hepatic failure, renal failure or multiorgan failure will be withdrawn from study treatment. Ensifentrine has been shown to be a likely substrate for BCRP in vitro. A review of steady state exposure from Phase 2b studies RPL554-CO-203 and RPL554-CO-205 including 128 patients taking concomitant BCRP inhibitors (e.g. proton pump inhibitors, pravastatin) has shown that there is no increase in exposure compared to patients not taking these classes of medications, therefore, concomitant use of BCRP inhibitors is not excluded.

4.4 Justification for Dose

Ensifentrine has been well-tolerated in clinical studies to date. The dose for this study (2 mg) was selected based on analysis of pharmacokinetic (PK) and pharmacodynamic (PD) data (lung function improvement) from single dose study with pMDI, combined with what is known about PK/PD from multiple studies with a nebulized suspension of ensifentrine in healthy volunteers and patients with COPD, and a clinical study using ensifentrine in dry powder inhaler format.

The dose was selected based on analysis of fine particle dose comparing the pMDI with a DPI and nebulized suspension of ensifentrine, along with pharmacokinetic (PK) and pharmacodynamic (PD) data (lung function improvement) from single dose study with pMDI RPL554-MD-201, combined with what is known about PK/PD from multiple studies with a nebulized suspension of ensifentrine in patients with COPD, and a clinical study using ensifentrine in dry powder inhaler format (RPL554-DP-201). These data support that a 2 mg twice daily dose of ensifentrine pMDI should provide equivalent fine particle dose, PK and lung function improvement as that observed from a twice daily 3 mg nebulized dose, which has shown to be efficacious and well-tolerated over 4 weeks in patients with COPD.

4.5 End of Study Definition

A patient is considered to have completed the study if he/she has successfully completed all visits during their treatment period while hospitalized and completed the Day 29 and Day 60 follow-up contacts.

The end of the study is defined as the date of the last follow-up visit of the last patient in the study.

5 STUDY POPULATION

Approximately 45 male and non-pregnant female adults hospitalized with COVID-19 and who meet all eligibility criteria will be enrolled at one site. The inclusion and exclusion criteria are listed in **Table 4** and **Table 5**, respectively.

5.1 Inclusion Criteria

Table 4. Inclusion criteria.

1	Capable of giving informed consent indicating that they understand the purpose of the study and study procedures and agree to comply with the requirements and restrictions listed in the informed consent form and in this protocol.
2	Age: Patient must be at least 18 years of age and less than or equal to 80 years of age at the time of informed consent.
3	Sex: Males are eligible to participate or females of non-childbearing potential or WOCBP who have a negative pregnancy test at screening are eligible to participate. WOCBP and female partners of male participants agree to either abstinence or use at least one primary form of highly effective contraception not including hormonal contraception from the time of screening through Day 60 following the first dose of study medication. Refer to Appendix 5.
4	Patient with a clinical status consistent with 3, 4 or 5 on the Ordinal scale and for whom the anticipated hospitalization is at least 72 hours (after randomization). • Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care • Hospitalized, requiring any supplemental oxygen • Hospitalized, requiring non-invasive ventilation or use of high flow oxygen devices
5	Admission to hospital AND have a confirmed diagnosis of severe acute respiratory syndrome coronavirus (SARS-COV-2) infection confirmed by polymerase chain reaction (PCR) test AND displays at least one of the following: a. Respiratory rate > 24 breaths per minute, b. new cough, c. new atypical chest pain, d. new dyspnea, e. oxygen saturation < 97% at rest, f. chest x-ray with new changes consistent with COVID- related airspace disease.
6	Capable of complying with all study restrictions and procedures including ability to use the pMDI correctly.

5.2 Exclusion Criteria

Table 5. Exclusion criteria.

1	Participation in any other clinical trial of an experimental treatment for COVID-19, unless related to an expanded access program as part of Standard of Care.
2	Evidence of multiorgan failure.
3	Requiring mechanical ventilation at screening.
4	Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 X upper limit of normal (ULN) at screening.
5	Creatinine clearance < 30 mL/min at screening.
6	Pregnancy or lactation at screening.
7	Allergy or other contraindication or one of ensifentrine.
8	In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments.
9	Use of prohibited medications (Section 6.5).
10	Any other reason that the Investigator considers makes the patient unsuitable to participate.

5.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but were not randomized to receive blinded study medication. Patients randomized in error but not treated should be withdrawn.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6 STUDY TREATMENT

6.1 Treatment Assignment

All patients consented will be assigned a patient identification number upon signing of the informed consent using the following convention: XXX-YYY where XXX is UAB's center number and YYY is the patient number (001, 002, etc.).

Once eligibility is confirmed, patients will be randomized in a 2:1 ratio to one of two treatment arms listed below (**Table 6**).

Table 6. Treatment arms.

Treatment Arm	n	Treatment
Treatment Arm 1	30	Blinded ensifentrine (2 mg) pMDI BID + SoC*
Treatment Arm 2	15	Blinded placebo pMDI BID + SoC*
Abbreviations: SoC= standard of care, pMDI= pressurized metered dose inhaler, BID= twice daily *SoC treatment for COVID-19 infection based on established practices within UAB		

Randomization will take place prior to the first study medication administration in the order patients are enrolled and in accordance with a computer-generated randomization list supplied by the statistician. Available randomization numbers must be used sequentially for the next enrolled patient. Patients will be dosed with either blinded ensifentrine or placebo according to the randomization scheme.

6.2 Administration of Study Medication

Under the direction of study staff, randomized patients will self-administer 4 actuations (puffs) pMDI at each dosing event. Dosing will be performed twice daily approximately 12 hours apart in the morning and evening at approximately the same time each day (**Table 7**).

The precise date and time of dose administrations performed in clinic at study visits, and in the evening, shall be documented in the eCRF. Information on missing doses will also be documented in the eCRF.

Table 7. Study medication dosing.

Time of day	Study medication dose
Morning	4 puffs via pMDI before noon
Evening	4 puffs via pMDI approximately 12 hours later
Abbreviations: pMDI= pressurized metered dose inhaler	

6.3 Investigational Product/Study Medication

6.3.1 Study medication dispensing

Study medication will be shipped to the site unblinded pharmacist from the Sponsor. Ensifentrine and placebo pMDIs are supplied as unlabeled, pressurized canisters with yellow plastic actuators. Inhalers will be packaged individually at the site in single cartons and labelled according to the randomization schedule. Appropriate study center personnel will dispense the appropriate double-blind medication. Clinical study labels will be added at the site pharmacy. Each inhaler provides approximately 15 days of treatment, thus, each patient will require 1 inhaler to be dispensed on Days 1, 12 and 24 to complete 29 days of treatment. Detailed dispensing instructions will be provided in the study Pharmacy Manual.

Study medication is kept with the site Pharmacy and not the patient, in accordance with site procedures.

6.3.2 Identity, preparation and labelling of study medication

The International Union of Pure and Applied Chemistry (IUPAC) name for ensifentrine drug substance is 9,10-dimethoxy-2-(2,4,6-trimethylphenylimino)-3-(N-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one. The ensifentrine pMDI is manufactured in accordance with Good Manufacturing Practice (GMP) guidelines.

6.3.3 Formulation information

The active formulations of ensifentrine and placebo in pMDI will be double-blind. The placebo is the same as the ensifentrine active formulation, except that the active ingredient is omitted. Each actuation of pMDI containing ensifentrine will deliver 0.5 mg, such that 4 puffs will equal a 2 mg dose.

The formulation constituent and concentrations are described in **Table 8**.

Table 8. Study medication composition.

Constituent	Ensifentrine Concentration (% w/w)	Placebo Concentration (% w/w)
Ensifentrine (micronized)	0.648	0
HFA-134a	99.352	99.352
Abbreviations: HFA=hydrofluoroalkane; w/w = weight per weight		

6.3.4 Preparation/Handling/Storage/Accountability

- Study medication should not be stored above 25°C. Temperature logs should be maintained in areas where study medication is stored. If temperature conditions have been compromised or any study medication has not been stored appropriately, this should be documented, and the study medication quarantined until the Sponsor has been notified and confirmed whether it may be used.
- Study medication will be stored under the control of the Investigator or designee in a secure facility appropriate for the advised storage conditions. Study

medications that are to be returned by the Investigator/staff or have expired must be stored separately from the unused study medications.

- The Investigator, a member of the study center staff, the site pharmacist, or pharmacy team member must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.
- The Investigator will be responsible for the labeling and dispensing, inventory and accountability of study medication, exercising accepted medical and pharmaceutical practices and ensuring that an accurate, timely record of the disposition is maintained.
    - The Investigator must ensure there is at least one unblinded pharmacist to label the study medication and perform accountability measures.
- At the end of the study, the unused study medication can be destroyed locally after accountability has been verified and written authorization has been provided by the Sponsor.

6.4 Emergency Unblinding

The blind will be broken only if specific emergency treatment would require knowing the treatment status of the patient or if the protocol review committee (Section 11) recommends unblinding data for safety review reasons. If the blind needs to be broken for an individual patient, the Investigator will contact the Sponsor as soon as feasible. The Investigator may unblind the study medication immediately if he/she feels it is necessary prior to contacting the Sponsor. However, the Investigator should promptly document and explain to the Sponsor any premature unblinding. Otherwise, all blinding will be maintained until all queries are resolved and the database is locked.

The statistical vendor for this study is the site's data management group and will have access to break the blind, if necessary, but this will be kept in a secure access area.

6.5 Concomitant & Prohibited Medications

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

- UAB's standard treatment for COVID-19 infection is permitted, with the exception of prohibited medications listed in **Table 9**.
- UAB's standard treatment for COVID-19 infection will be recorded in the eCRF from screening to discharge.

Table 9. Prohibited concomitant medications.

Medication	Time Interval
Theophylline, PDE4 inhibitors (e.g. roflumilast, apremilast, crisaborole)	48 hours prior to Screening Visit and prohibited during the study
Investigational or experimental medication for COVID-19 infection as part of a clinical trial that is not considered Standard of Care	During study participation
Abbreviations: PDE= phosphodiesterase	

6.5.1 Recording use of concomitant medications

- Documentation during screening should be recorded on the concomitant medication page along with reason for use, dates of administration (start and end dates), and dosing information (dose and frequency). End date should be documented as "Ongoing."
- Details (e.g., dose, route, date, and time of administration) will be recorded.
- All medications for each subject along with the reason for use, time/date of administration, dose, route and duration of their administration will be recorded starting at screening and changes recorded during the trial.

7 DISCONTINUATION/WITHDRAWAL OF PATIENTS OR STUDY TERMINATION

7.1 Discontinuation of Study Medication

Patients may choose to permanently discontinue study medication before the end of the trial. The Investigator may choose for the patient to permanently discontinue study medication before the end of the trial at their discretion. The Investigator must document the reason for discontinuation of study medication.

Study medication discontinuation may occur due to:

- Unacceptable toxicity related to study treatment
- Intolerable or persistent adverse events of any severity
- General or specific changes in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the Investigator
- The request of the patient

Patients who permanently discontinue study medication are not required to withdraw from the study. Ideally, subjects who have permanently discontinued study medication will continue to complete important efficacy and safety assessments through the follow-up contact.

- If a patient withdraws from the study and has received at least one dose of the study medication they may:
    - continue in the study without taking study medication and complete important efficacy and safety assessments through the follow up contact, or
    - continue to allow the study to record data associated with their standard treatment course without completing any study required assessments with the exception of the follow up contact, or
    - participate in the follow up phone calls only approximately 30 and 60 days after enrolling in the study

7.1.1 Study specific discontinuation of study medication criteria

Patients should be withdrawn from study medication for the following reasons:

- If they experience a clinically significant progression of disease such as:
    - Kidney or liver or multi-organ failure
    - Need for mechanical ventilation
    - Stage 5, end stage kidney disease (GFR <15 mL/min)
    - ALT and/or AST increases to > 5 times upper limits of normal
- Pregnancy in a female patient
- If a patient who does not meet eligibility criteria is inadvertently randomized and received study medication

Other criteria that may or may not require permanent discontinuation of study medication include but are not limited to:

Adverse event, lack of efficacy, protocol deviation, non-compliance, study closed/terminated, investigator discretion, or patient withdrawal of consent.

7.2 Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request, may permanently discontinue study medication but wish to remain in the study, or may be withdrawn from administration of study medication or from all study participation at the discretion of the Investigator at any time for safety, behavioral, compliance, or administrative reasons.

Withdrawn patients may need to be replaced, depending on the actual discontinuation rate.

See the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.

7.3 Lost to Follow-up

- A patient will be considered lost to follow-up if he or she is unable to be contacted by the study center.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient. These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, a telephone call to medical contacts listed in medical record will be performed to determine vital status. If dead – marked as death and date recorded. If unreachable, a vital records check may be conducted to determine if a death has occurred approximately 60 days following the 1st dose of study medication.
- If no death record is found and the patient or medical contact continues to be unreachable approximately 60 days following the 1st dose of study medication, he/she will be considered to have been lost to follow-up and withdrawn from the study.

7.4 Termination of the Study

Given the potential severity of COVID-19 and limited information about the expected clinical course, there are no pre-specified study stopping rules. Instead there will be close oversight by the protocol team composed of the Sponsor's Medical Monitor, the Investigator and 2 independent physicians, and frequent reviews of the safety data (Section 11).

Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study;
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of ensifentrine;
- Serious failure of the Investigator to comply with the International Council on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP) or local regulations;
- Submission of knowingly false information from the research facility to the Sponsor, the Independent Ethics Committee (IEC) or any national regulatory officials;
- Major, repeated, non-adherence to the protocol.

The Sponsor must be informed immediately in the event of any major protocol deviation or serious breach of ICH GCP.

Study termination and follow-up will be performed in compliance with the conditions set forth in ICH GCP. The decision to discontinue the study is at the discretion of the Sponsor, the Investigator, the regulatory authority or IEC and should if possible be taken by mutual agreement. A record of such a discussion will be prepared and stored in the study file. The Sponsor will ensure the regulatory authorities and IECs are notified.

8 STUDY ASSESSMENTS AND PROCEDURES

- The SoA is in Section 1.3.
- Protocol amendments, waivers or exemptions are discussed in Section 9. Regulatory, ethical and study oversight details are included in Appendix 2.
- Safety concerns related to use of the study medication should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study medication. The Investigator may discontinue study medication for a patient if deemed necessary. The treatment of any given subject may be stopped for SAEs, clinically significant adverse events, severe laboratory abnormalities, or any other medical conditions that indicate to the Investigator that continued dosing is not in the best interest of the patient. In addition, a subject in this clinical study may discontinue study drug at their request for any reason.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct as well as compliance discussed in Section 9 and Appendix 2 and regulatory requirements included in Appendix 2.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected for study related procedures from each patient, will not exceed 500 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Should a death occur in a study patient, data should be collected on whether the death occurred after withdrawal study medication and, if so, the reason for study drug withdrawal. Withdrawal of care, comfort care, do not resuscitate (DNR) orders will be captured in the event of a death.
- The site will attempt to follow-up on clinical status, but at a minimum the vital status of patients that do not have a telephone follow-up approximately 60 days following randomization and at least one dose of study medication.
- See Section 5.3 for specific information to be collected for screen failures.

8.1 Collection of Data

Patients will be assessed daily while hospitalized. Clinical data will be recorded using eCRFs adapted from the WHO-ISARIC (World Health Organization–International Severe Acute Respiratory and Emerging Infections Consortium) case record form (https://isaric.tghn.org).

Screening and baseline information will be collected and recorded on the eCRF. This will include the following information:

- Informed consent review, eligibility review, including screening liver, kidney and pregnancy (if applicable) laboratory tests, and categorization of their positive COVID-19 disease severity (according to the FDA's document: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry, May 2020). Refer to Section 8.1.2 for severity definitions.
- Demographics, hospital admission date (for COVID-19 infection), medical and smoking history, standard of care medications and treatments and type of facility transferred from.
- Existing co-morbidities and any medication taken for those listed as well as medications taken since admission.

Randomization information will be recorded on an eCRF. If study medication is dispensed, it will be recorded on this form.

Starting on Day 1 to discharge, Day 29 or withdrawal of consent, site staff will record on an eCRF daily the following information:

- Clinical status (7-point ordinal scale) each morning (Section 8.1.1).
- Vital signs each morning at approximately the same time (Section 8.1.3).
- Concomitant medications taken as part of SoC for COVID-19 infection treatment (Section 6.5.1 and Section 8.1.4).
- Supportive treatments received as part of SoC for COVID-19 infection treatment or new infection that develops while hospitalized (Section 8.1.4).
- Routine laboratory, infection and imaging test results received as part of SoC (Section 8.1.4).
- Study medication doses taken and when.
- On the day of discharge or Day 29, safety laboratory tests may be performed at the discretion of the treating physician and, if completed, may be completed within 24 hours of the patient's discharge from the hospital.
- Adverse events.

At discharge site staff will schedule a follow-up and complete an eCRF page including the following:

- Date of discharge and reason (e.g., COVID-19 negative, improved enough for discharge, etc.)
- Where the patient was discharged to (e.g., home, rehab center, etc.)
- If the patient was COVID-19 positive or negative at discharge (yes/no/unknown)
- Which medications the patient was discharged with
- If supplemental oxygen or other supportive treatment was prescribed for treatment after discharge

At the follow-up calls, site staff will complete eCRF pages including the following:

- Date of follow-up

- How patient is doing, their clinical (7-point ordinal scale) or minimally recording their vital status.
- Whether the patient had been re-hospitalized following discharge.
- Any adverse events or pregnancy
- A disposition eCRF for how the patient completed or did not complete (with reason) the study.

8.1.1 7-point ordinal scale of clinical improvement

Clinical status will be assessed using a 7-point ordinal scale. The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded (i.e., on Day 3, Day 2 score is obtained and recorded as Day 2). The ordinal scale is adapted from the WHO R&D Blueprint expert group which measures illness severity over time (https://www.who.int/blueprint/priority-diseases/key-action/COVID19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf). The scale is listed in **Table 10**.

Table 10. 7-point ordinal scale.

1	not hospitalized, no limitations of activities
2	not hospitalized, limitation of activities, home oxygen requirement, or both
3	hospitalized, not requiring supplemental oxygen but requiring ongoing medical care
4	hospitalized, requiring any supplemental oxygen
5	hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices
6	hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and
7	death

8.1.2 Categorizing COVID-19 disease severity

Categorization of PCR positive COVID-19 disease severity will be in accordance with the FDA's document: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry (May 2020). Patients with Critical Disease would meet exclusion criteria and not eligible for participation.

- **Mild** disease (meeting all inclusion and no exclusion criteria): Symptoms of mild illness that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea and no clinical signs indicative of moderate, severe, or critical severity.
- **Moderate** disease (meeting all inclusion and no exclusion criteria): could include any symptom of mild illness or shortness of breath with exertion. Clinical signs suggestive of moderate illness, such as respiratory rate ≥ 20 breaths per minute,

saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute and no clinical signs indicative of severe or critical severity.

- **Severe** disease (meeting all inclusion and no exclusion criteria): could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress. Clinical signs indicative of severe systemic illness, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 and no criteria of critical severity.
- **Critical** disease: evidence of critical illness, defined by at least one of the following: 1) respiratory failure defined based on resource utilization requiring at least one of the following: endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation); 2) shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors); or 3) multi-organ dysfunction/failure.

8.1.3 Vital sign assessment

Vital signs will be assessed and recorded each morning at approximately the same time of a given study day.

Vital signs to be assessed and recorded include: respiration rate (breaths per minute), oxygen saturation, supplemental oxygen use (yes/no), fraction of inhaled oxygen (FiO2), sternal capillary refill time, body temperature, dehydration, blood pressure, heart rate (beats per minute and level of consciousness graded on the AVPU scale (Alert, Verbal = voice response present, Pain = pain response present, Unresponsive) (worst score on the assessment day for each).

8.1.4 Recording SoC medications, treatments & laboratory test results

Concomitant medications/therapy will be recorded daily (Section 6.5). The list of prohibited medications/therapy is provided in Section 6.5. Concomitant medications taken as part of SoC for COVID-19 infection treatment, and which may include: angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, antibiotics, anti-fungal agents, anti-viral agents (e.g., remdesivir), inhaled or oral corticosteroids, immune-suppressant agents, intravenous fluids, non-steroidal anti-inflammatory agents, or oral/orogastric fluids, or other medications (as specified).

Status of supportive treatments received as part of SoC for COVID-19 infection treatment will be recorded daily (yes/no and details as applicable in the eCRF). These may include treatments such as: oxygen therapy and details, high flow oxygen use, non-invasive ventilation, invasive ventilation, prone positioning, inhaled nitric oxide, tracheostomy inserted, ECLS/ECMO, renal replacement therapy or dialysis, vasopressor/inotropic agent use, use of neuromuscular blocking agents, other interventions or procedures (specified). Any blood gas analyses and results and any new infection occurring during participation, regardless of organism (i.e. viral or non-viral), should be captured along with the site of infection and source of culture (e.g., BAL, tracheal aspirate, sputum, blood, urine etc.).

Routine laboratory and imaging tests performed as recommended by the treating physician (refer to Appendix 3) will be recorded as they are performed. Some tests may be recorded more frequently (e.g., white blood cell count, neutrophil count, lymphocyte count, creatinine values) than others (e.g., inflammatory markers and liver function tests).

8.2 Screening/baseline and Day 1

Activities related to the screening/baseline and Day 1 visits are listed in **Table 11** and **Table 12**. The Screening/baseline eCRF and the Daily eCRF must be completed pre-randomization and pre-study medication dose (if applicable).

Table 11. Screening/baseline visit activities.

Assessment	Information
Informed Consent	• Informed consent must be obtained according to the Informed Consent Process described in Appendix 2. • Counsel subjects to use adequate birth control methods required during the trial to avoid pregnancy. • Women of childbearing potential must agree to abstinence or to use at least one primary form of contraception for the duration of the study. Patients who are randomized must continue this for 60 days following the first dose (acceptable methods will be determined by the site).
Demographic variables	• Document the patient's demographic variables will include items such as age, sex, ethnicity, height, weight, body mass index, and race.
Medical, surgical and smoking history	• Document the patient's history of relevant current or past medical conditions, surgical history, and smoking history (current or former [yes or no]) will be obtained. Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening. • Minor surgical procedures (e.g., tonsillectomy, appendectomy) performed more than 5 years prior to Screening do not need to be recorded. • Medical condition(s) identified during Screening will be documented as medical history and not as an adverse event(s) unless the condition worsens during the trial and meets the definition of an adverse event.
Hospital admission information	• Document the reason for hospital admission (e.g., COVID-19 symptoms and diagnosis). Refer to Inclusion criteria in Section 5.1. • Document the most recent laboratory and imaging (radiology, hematology, chemistry, serology, urine, etc.) test results since hospital admission (Section 8.1.4).

SoC concomitant medication & supportive treatment assessment	• SoC concomitant medications and administered treatments must be recorded (Section 8.1.4). • Document the medications taken (for COVID-19 treatment) since admission along with the time, dose, and duration of their administration.
Brief physical examination	• Document the results of a physical examination performed within 4 days of randomization. • Assess the patient's heart and lungs and document.
Safety laboratory assessments	• Perform Screening Hematology, Chemistry (non-fasting), Urine Analysis, Serum Pregnancy Test (as applicable) and document findings (see Appendix 3 and Exclusion criteria in Section 5.2).
Inclusion/Exclusion criteria	• Assess eligibility of the patient eligibility using the Inclusion (Section 5.1) and Exclusion criteria (Section 5.2). • Categorization of disease severity (Section 8.1.2).
Clinical status assessment (7-point ordinal scale)	• Clinical status will be assessed and recorded using the 7-point ordinal scale at the first assessment of a given study day. • See Section 8.1.1.
Vital sign assessment	• Vital signs will be assessed and recorded each morning at approximately the same time of a given study day. • See Section 8.1.3.

Day 1 may take place on the same day as the screening/baseline visit, if appropriate. If Day 1 activities take place on the same day as screening/baseline visit, only one 7-point ordinal scale assessment and vital signs are necessary, but they must be completed prior to dosing, if the patient is randomized to Treatment Arm 1.

Table 12. Day 1 visit activities.

Assessment	Information
Randomization	• Patients meeting all Inclusion criteria (Section 5.1) and none of the Exclusion criteria (Section 5.2) will be randomly assigned to one treatment arm prior to study medication treatment.
SoC concomitant medication & supportive treatment assessment	• SoC concomitant medications and administered treatments must be recorded (Section 8.1.4). • Document any care decisions that are made due to resource limitation.
Clinical status assessment (7-point ordinal scale)	• Clinical status will be assessed and recorded using the 7-point ordinal scale at the first assessment of a given study day. • See Section 8.1.1.
Vital sign assessment	• Vital signs will be assessed and recorded each morning at approximately the same time of a given study day. • See Section 8.1.3.

Blinded study medication dispensing	• Study medication dispensed by study staff.
Blinded study medication training	• pMDI Observation & Training by study staff.
Blinded study medication dosing	• Blinded study medication administered via pMDI in the morning (4 puffs) and approximately 12 hours later in the evening (4 puffs). • Document date and time taken.
Adverse Events assessments	• The method of detecting adverse event will be performed as described in Section 8.6 and Appendix 4.

8.3 Study Treatment & Day of Discharge from Hospital

Activities related to Days 2-29 or until discharge are listed in **Table 13**. At each daily visit, the Daily eCRF must be completed.

Table 13. Days 2-29 or until discharge daily activities.

Assessment	Information
SoC concomitant medication & supportive treatment assessment	• Taken as prescribed and recorded daily, as above for Day 1. • Any new infection occurring during participation, regardless of organism (i.e. viral or non-viral), should be captured. Additionally, the site of infection and source of culture (e.g., BAL, tracheal aspirate, sputum, blood, urine etc.) should be recorded.
SoC laboratory results	• Routine laboratory and imaging tests performed as recommended by the treating physician (Section 8.1.4 and Appendix 3).
Clinical status assessment (7-point ordinal scale)	• Assessed and documented daily, as above for Day 1.
Vital sign assessment	• Assessed and documented daily, as above for Day 1.
Blinded study medication dispensing & collection	• Blinded study medication dispensed and collected by study staff on Days 12 and 24 and discharge. • Dispensing and collection data is documented.
Blinded study medication dosing	• Taken daily, as above for Day 1. On the Day of Discharge, study medication may be dosed as deemed appropriate by Investigator. • Document date and time taken.
Adverse Events assessments	• Assessed and recorded daily, as above for Day 1.

8.4 Discharge Activities

For the Day of Discharge (Day 29 or the last day in the hospital if discharged before Day 29), the Daily eCRF will be completed as above (**Table 13**) as well as a Discharge eCRF to document how the patient was discharged (**Table 14**).

Table 14. Day of discharge activities.

Assessment	Information
Record discharge information	• Discharged (yes/no).* • If discharged, the Date of discharge and reason (e.g., COVID-19 negative, recovered, not discharged [remains hospitalized] etc.) is noted. Date of scheduled follow-up telephone call. • Where the patient was discharged to (e.g., home, rehab center, etc.). • If the patient was COVID-19 positive or negative at discharge (yes/no/unknown). • Which medications the patient was discharged with. • If supplemental oxygen was prescribed for treatment after discharge.

*** Patients not discharged from the hospital by Day 29**

Some study patients may not be ready for discharge from the hospital by Day 29. In these instances, study treatment and data collection procedures still end on Day 29 (with the exception of contacts in the next section). This information will be noted in the Discharge eCRF as "study treatment complete, but patient remains hospitalized." This would also be captured in the Day 29 Clinical status assessment (7-point ordinal scale).

Patients that remain hospitalized after Day 29 will be contacted as described in the next section.

8.5 Post Discharge/Day 29 Contacts

Following Day 29 or discharge from the hospital (if earlier), there will be three points of contact with all study patients, regardless of hospitalization status. Each contact will require the completion of a Follow-up eCRF (**Table 15**).

- Discharge Contact: 4 to 10 days after discharge from hospital, if discharged within the 29-day treatment period.
    - If the patient remains hospitalized after Day 29, study treatment and data collection procedures still end on Day 29 (with the exception of contacts in this section) and contact with the patient will take place 4 to 10 days after receipt of last dose of study medication (Day 29).
- Day 29 Contact: 26 to 32 days after first dose of study medication. If the Discharge Contact and Day 29 Contact fall within same window, this contact will be combined to the Day 29.

- Day 60 Follow-up: 55 to 65 days after first dose of study medication.
    - Should a patient or their medical contact be unable to be contacted at any of these timepoints, a vital records search will be performed to determine the patient's vital status approximately 60 days after first dose of study medication.

Table 15. Post-discharge follow-up activities.

Assessment	Information
Follow-up date	• Date of follow-up contact
Clinical status assessment (7-point ordinal scale)	• Assessed and documented, as above for Day 1 (clinical and vital status)
Re-hospitalization status or remains in hospital	• Any incidence of re-admission to the hospital following a 24-hour period of discharge (date and duration) that is related to COVID-19 • Date of discharge (if after Day 29) should be noted in the Follow-up eCRF.
Adverse Events assessments	• Documented, as above for Day 1

8.6 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4. The SoA is Table 3 in Section 1.3.

Adverse events will be reported by the patient and/or investigator and recorded on the AE CRF.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study medication or study procedures, or that caused the patient to discontinue the study (Appendix 4).

As stated in Section 8.6, medical condition(s) identified during the screening visit will be documented as medical history and not as an adverse event(s) unless the condition worsens during the trial and meets the definition of an adverse event.

8.6.1 Time period and frequency for collecting AE and SAE information

For this study, AEs and SAEs will be collected from the time of the first dose of study medication through the follow-up (end of study) visit.

SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests or change in existing therapy) will be collected from the time of consent through the follow-up visit.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor designee within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study medication or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.6.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.6.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, through the follow-up visit, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up of AEs and SAEs are given in Appendix 4.

8.6.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study medication under clinical investigation are met. The Investigator will submit any updated SAE data to the Sponsor designee within 24 hours of it being available.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study medication under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.6.5 Pregnancy

- Details of all pregnancies in female patients will be collected after the start of study medication and until 30 days after the last dose of study medication.

- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.6.6 Adverse Events of special interest

Adverse events of special interest have not been identified for ensifentrine.

8.7 Treatment of Overdose

An overdose is defined as a dose greater than the total daily doses prescribed in this study which results in clinical signs and symptoms. These should be recorded by the investigator on the AE/SAE pages.

In the event of an overdose the investigator should use clinical judgement in treating the overdose and contact the study medical monitor. Verona Pharma is not recommending specific treatment guidance for overdose and toxicity management.

9 PROTOCOL EXEMPTIONS/WAIVERS

The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

- The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

  (a) To the IRB/IEC for review and approval/favorable opinion;

  (b) To the sponsor for agreement and, if required;

  (c) To the regulatory authority(ies)

Regulatory, ethical and study oversight details are included in Appendix 2.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

All analyses are considered exploratory and hypothesis-generating. All tests will be two-sided at 5% significance level. Hypothesis tested for the primary endpoint will be if addition of ensifentrine to SoC for up to 29 days could increase the proportion of patients with recovery versus standard of care plus placebo. The status according to the 7-point ordinal scale of all patients regardless of treatment withdrawal will be followed up during the scheduled treatment period (Day 29) and at a follow-up Day 60, or as far as possible. Secondary endpoints are tested independently and there will be no adjustment for multiple tests.

Study days for analyses include Day 1 (start dose), Day 7 (6 to 8 days after 1st dose), Day 14 (13 to 15 days after 1st dose) and Day 29.

10.2 Study Populations

Modified intent to treat (mITT):

- Will consist of all randomized and treated patients. Efficacy will be evaluated as randomized.

Per protocol population (PP):

- Will consist of all patients in mITT without any major protocol deviations deemed to have an effect on efficacy analyses.

Safety set (SS):

- Will consist of all randomized and treated patients. Safety will be evaluated by actual treatment.

10.3 Sample Size Determination

This is a pilot study and it is not powered based on any specific endpoint. Sample size has been set to minimize the number of patients exposed, but still large enough to give reliable estimates on the efficacy and safety of ensifentrine in the target population.

10.4 Efficacy

The proportion of patients with recovery at Day 29 will be compared between treatment groups using a logistic regression model adjusting for treatment. The treatment difference will be expressed as an odds ratio with 95% confidence intervals and associated two-sided p-value. Potential stratification variables such as age group and/or gender may be considered depending on the randomization outcome, details will be given in the Statistical Analysis Plan.

The time to recovery from Day 1 to Day 29 will be compared between treatment groups using a log-rank test; patients not in recovery at end-of study/withdrawal will be censored at last observed time point in the treatment period or at last time status was assessed if collected post treatment-withdrawal. Patients with death as outcome will be censored at the scheduled end-of-study day 29. Data will be illustrated using Kaplan-Meier plots and

the median time to recovery estimated if appropriate. Stratification in the model with respect to age group and/or gender may be considered based on the randomization outcome.

Secondary endpoints of survival type will be compared between treatments using the log rank test similar to the time to recovery endpoint. Secondary endpoints assessing proportion of patients fulfilling an event will be compared between treatments using a logistic regression. Continuous outcomes will be compared between treatments using ANCOVA models with treatment and stratification groups as factors and baseline as a covariate. Estimated treatment difference with 95% confidence intervals and associated 2-sided p-value will be given. Endpoints assessing duration of (days with) additional oxygen use/ventilator need will be compared between treatments using Wilcoxon rank sum test.

10.5 Safety

Safety endpoints include SAEs and AEs (Appendix 4). Adverse events will be analyzed using quantitative and qualitative measures. Treatment-emergent adverse events will be summarized by treatment group for all AEs, related AEs, serious adverse events, deaths, adverse events leading to discontinuation of study medication or to withdrawal from study, adverse events of different severity and adverse events of different chronicity. Treatment-emergent adverse events will be coded using MedDRA and summarized by system organ class and preferred term for each treatment group. For selected adverse events, time to first event may be visualized using Kaplan-Meier plots and tested between treatment using the log-rank test.

Available laboratory data will be summarized by each visit including change from baseline. The number of normal, abnormal not clinically significant and abnormal clinically significant values on each parameter will be summarized for change over study using shift tables. All data will be listed and values outside reference ranges will be highlighted in the listings.

Vital signs will be summarized by each visit including change from baseline. All data will be listed and values outside reference ranges will be highlighted in the listings.

10.5.1 Missing Data

The patients withdrawn from treatment will be followed up regarding their status according to the 7-point ordinal scale at Day 29 as far as possible (exceptions for patients with withdrawn consent or lost to follow-up) and this data will be the primary source for handling missing data in the study. Status on the 7-point scale, including vital status, will also be collected at the Day 60 follow-up. In survival analysis, patients with death as outcome will be censored at Day 29 (Day 60), unless the required event was reached prior to death. In analyses of oxygen need, patients in ventilator care or with death as outcome will be considered in oxygen need. In analyses of ventilator need, patient with death will be considered in ventilator need. Further details on imputation will be given in the Statistical Analysis Plan.

10.6 Interim Analyses

There will be no formal interim analysis in the study.

11 DATA MONITORING COMMITTEE

Ensifentrine has been studied in over 1000 patients with COPD, which is a group known to have severely compromised lung physiology and multiple comorbidities, including in over 600 patients for 4 weeks duration. Because the safety profile in this population has been shown to be similar to placebo over the maximal study duration and expected exposure for this study with a 2 mg twice daily pMDI dose is similar to that expected from a twice daily 3 mg nebulized dose in COPD patients, a formal data safety monitoring board is not planned.

This is a single site study with a small number of patients. Given the potential severity of COVID-19 and limited information about the expected clinical course, a protocol team composed of the Sponsor's Medical Monitor, the Investigator and 2 independent physicians, will review blinded pools of AE data at regular intervals (approximately every 10 patients randomized) to evaluate whether a significant number of unexpected AEs are occurring (AEs that do not fit with the known course of COVID-19).

If there are a significant number of unexpected AEs, the protocol team will be asked to review unblinded safety data in an ad hoc meeting. The committee can recommend dose reduction, or stopping the study for safety or unblinding concerns. The study will not stop enrollment awaiting these reviews, although the protocol team may recommend temporary or permanent cessation of enrollment based on their safety reviews.

12 REFERENCE LIST

1 Abbott-Banner KH, Page CP. Dual PDE3/4 and PDE4 inhibitors: novel treatments for COPD and other inflammatory airway diseases. Basic Clin Pharmacol Toxicol. 2014 May; 114 (5): 365-76. doi: 10.1111/bcpt.12209.

2 Bjermer L, Abbott-Banner K, Newman K. Efficacy and safety of a first-in-class inhaled PDE3/4 inhibitor (ensifentrine) vs salbutamol in asthma. Pulm Pharmacol Ther. 2019 Oct; 58: 101814. doi: 10.1016/j.pupt.2019.101814.

3 Boswell-Smith V, Spina D, Oxford AW, Comer MB, Seeds EA, Page CP. The pharmacology of two novel long-acting phosphodiesterase 3/4 inhibitors, RPL554 [9,10-dimethoxy-2(2,4,6-trimethylphenylimino)-3-(n-carbamoyl-2-aminoethyl)-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinolin-4-one] and RPL565 [6,7-dihydro-2-(2,6-diisopropylphenoxy)-9,10-dimethoxy-4H-pyrimido[6,1-a]isoquinolin-4-one]. J Pharmacol Exp Ther. 2006 Aug; 318 (2): 840-8. DOI: 10.1124/jpet.105.099192.

4 Edwards MR, Facchinetti F, Civelli M, et al. Anti-inflammatory effects of the novel inhaled phosphodiesterase type 4 inhibitor CHF6001 on virus-inducible cytokines. Pharmacol Res Perspect. 2016 Jan 15;4(1): e00202. doi: 10.1002/prp2.202.

5 Franciosi LG, Diamant Z, Banner KH, Zuiker R, Morelli N, Kamerling IM, de Kam ML, Burggraaf J, Cohen AF, Cazzola M, Calzetta L, Singh D, Spina D, Walker MJ, Page CP. Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. Lancet Respir Med. 2013 Nov; 1 (9): 714-27. doi: 10.1016/S2213-2600(13)70187-5.

6 Gianello V, Salvi V, Parola C, et al. The PDE4 inhibitor CHF6001 modulates pro-inflammatory cytokines, chemokines and Th1- and Th17-polarizing cytokines in human dendritic cells. Biochem Pharmacol. 2019 May; 163:371-380.

7 Gong J, Dong H, Qing Xia S, et al. Correlation Analysis Between Disease Severity and Inflammation-related Parameters in Patients with COVID-19 Pneumonia. Med Rxiv 2020.02.25.20025643; doi: https://doi.org/10.1101/2020.02.25.20025643.

8 Mata M, Martinez I, Melero JA, et al. Roflumilast Inhibits Respiratory Syncytial Virus Infection in Human Differentiated Bronchial Epithelial Cells. PLoS One. 2013; 8(7): e69670. doi: 10.1371/journal.pone.0069670.

9 Matera MG, Page C, Cazzola M. PDE inhibitors currently in early clinical trials for the treatment of asthma. Expert Opin Investig Drugs. 2014 Sep; 23 (9): 1267-75. doi: 10.1517/13543784.2014.921157.

10 Pedersen S. Inhalers and nebulizers: Which to choose and why? Respiratory Medicine, 1996; 90: 69-77.

11 Savelikhina I, Ostrovskyy M, Ostrovska K, et al. Proinflammatory cytokine IL-6 detection in severe COPD patients: Focus on roflumilast. European Respiratory Journal 2018 52: OA3267; DOI: 10.1183/13993003.congress-2018.OA3267.

12 Singh D, Abbott-Banner K, Bengtsson T, Newman K. The short-term bronchodilator effects of the dual phosphodiesterase 3 and 4 inhibitor RPL554 in

COPD. Eur Respir J. 2018 Nov 1; 52 (5). pii: 1801074. doi: 10.1183/13993003.01074-2018.

13 Singh D, Martinez FJ, Watz H, Bengtsson T, Maurer BT. A dose-ranging study of the inhaled dual phosphodiesterase 3 and 4 inhibitor ensifentrine in COPD. Respir Res. 2020 Feb 10;21(1):47. doi: 10.1186/s12931-020-1307-4.

14 Turner MI, Matthes E, Billet A, et al. The dual phosphodiesterase 3 and 4 inhibitor RPL554 stimulates CFTR and ciliary beating in primary cultures of bronchial epithelia. Am J Physiol Lung Cell Mol Physiol. 2016 Jan 1;310(1): L59-70. doi: 10.1152/ajplung.00324.2015.

15 Verona Pharma plc. Ensifentrine Clinical Investigators Brochure v. 19.0. 20th May 2020.

16 WHO ordinal scale: Coronavirus disease (COVID-2019) R&D. Geneva: World Health Organization (http://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/).

17 WHO-ISARIC (World Health Organization–International Severe Acute Respiratory and Emerging Infections Consortium) case record form (https://isaric.tghn.org). Licensed under a Creative Commons Attribution-Share A like 4.0 International License by ISARIC on behalf of Oxford University.

18 Zuo H, Cattani-Cavalieri I, Musheshe N, Nikolaev VO, Schmidt M. Phosphodiesterases as therapeutic targets for respiratory diseases. Pharmacol Ther. 2019 May; 197: 225-242. doi: 10.1016/j.pharmthera.2019.02.002.

13 APPENDICES

Appendix 1: Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BAL	Bronchoalveolar Lavage
BID	Twice Daily
CBC	Complete Blood Count
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
Cmax	Maximum Serum Concentration
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
GCP	Good Clinical Practice
HBE	Human Bronchial Epithelial
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB/IEC	Institutional Review Board/Ethics Committee
LFT	Liver Function Tests
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
mL	Milliliter
nM	Nanomolar
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PDE4	Phosphodiesterase 4
PK	Pharmacokinetics
pMDI	Pressurized Metered Dose Inhaler
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event

SoA	Schedule of Activities
SoC	Standard of Care
SpO2	Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAB	University of Alabama at Birmingham
ULN	Upper Limit of Normal
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organization

Appendix 2: Regulatory, Ethical, and Study Oversight Consideration

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH Good Clinical Practice (GCP) Guidelines.
  - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC and Regulatory Healthy Authority and reviewed and approved before the study is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority approval, when applicable, before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the study center and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, EU Clinical Trials Directive 2001/20/EC (if applicable), and all other applicable local regulations.
- After reading the protocol, the Principal Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or designee (Appendix 6). The study will not start at any study center at which the Investigator has not signed the protocol.

Adequate Resources

The Investigator is responsible for supervising any individual or party to whom the Investigator delegates study-related duties and functions conducted at the study center.

If the Investigator/institution retains the services of any individual or party to perform study related duties and functions, the Investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

Financial arrangements are detailed in the Investigator Agreement between the Sponsor and Investigator.

The Sponsor will arrange clinical study insurance to compensate patients for any potential injury or death caused by the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the patient and/or the patient's legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the patient was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- A copy of the original ICF(s) must be provided to the patient or the patient's legally authorized representative.
- ICF New Information: New information since the time of the original consent can be presented to patients in format(s) or method(s) including, but not limited to those listed below unless excluded by local requirements:
  - Revised consent document
  - Addendum to consent
  - Memo or other communication to subjects
  - Orally by phone or in person

Documentation of the method the new information was presented to the patient along with the name of the site staff member and date the new information was presented to the patient must be documented in the patient's source document.

Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
- The Sponsor/Sponsor's designee will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.

Administrative Structure

Table 16. Study administrative structure.

Function	Responsible Organization
Study Operations Management	Verona Pharma
Medical Monitoring	Verona Pharma
Safety Reporting	IQVIA
Study Master File	Verona Pharma
Randomization Code	UAB
Data Management	UAB
Clinical Supply Management	Verona Pharma
Quality Assurance Auditing	Verona Pharma
Biostatistics	UAB
Medical Writing	Verona Pharma
Laboratory Assessments	UAB

Table 17. Medical monitor.

Primary Medical Monitor:	Kathleen Rickard, MD Chief Medical Officer, Verona Pharma 8045 Arco Corporate Drive, Suite 130 Raleigh, NC 27617 T- +1 646 740-7081 E- kathleen.rickard@veronapharma.com
24-hour Urgent Medical Contact	Kathleen Rickard, MD

Dissemination of Clinical Study Data

For studies conducted in the United States, the results of the study are required to be reported on clinicaltrials.gov no later than 1-year after the primary completion date of the clinical trial, which is defined as the date of final data collection for the primary outcome measure.

Data Quality Assurance

- All patient data relating to the study will be recorded on printed or eCRFs unless transmitted to the Sponsor or designee electronically (e.g. laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct and will need to confirm that the blinding procedures have or have not been maintained for each patient by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized study center personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g. via an audit trail).

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study center.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in ICH E6(R2) Section 1.51.

Study and Study Center Closure

The Sponsor reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of patients by the Investigator.
- Discontinuation of further study medication development.

Publication Policy

The data generated by this study are confidential information of the Sponsor.

Appendix 3: Laboratory Tests

Specified laboratory tests conducted as part of COVID-19 standard of care will be recorded in the electronic case record as these are conducted. The laboratory reports must be filed with the source documents.

The following safety laboratory tests are required for eligibility verification and upon discharge at the discretion of the treating physician and, if completed, may be completed within 24 hours of the patient's discharge from the hospital if not already conducted as part of standard of care:

- Alanine Aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT) (U/L)
- Aspartate Transaminase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT) (U/L)
- Creatinine (µmol/L)
- Serum pregnancy testing (as applicable)

Standard of care laboratory tests may include:

- Activated partial thromboplastin ratio (APTR)
- Activated partial thromboplastin time (APTT) (seconds)
- ALT/SGPT (U/L)
- AST/SGOT (U/L)
- Basic metabolic panel (BMP)
- C-reactive protein (CRP) (mg/L)
- Creatine kinase (U/L)
- Creatinine (µmol/L)
- D-dimer (mg/L)
- Ferritin (ng/mL)
- Glucose (mmol/L)
- Hematocrit (%)
- Hemoglobin (g/L)
- Interleukin 6 (IL-6) (pg/mL)
- International normalized ratio (INR)Troponin I (ng/mL)
- Lactate (mmol/L)
- Lactate dehydrogenase (LDH) (U/L)
- Lymphocyte count (109/L)
- Neutrophil count (109/L)
- Platelets (x109/L)
- Potassium (mmol/L)
- Procalcitonin (ng/mL)
- Prothrombin time (PT) test (seconds)
- Sodium (mmol/L)
- Total bilirubin (µmol/L)
- Urea (BUN) (mmol/L)
- White blood cell (WBC) count (x109/L)

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of AE

- An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study medication, whether or not considered related to the study medication.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.
- Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

Events Meeting the AE Definition

- Any abnormal laboratory test results (e.g., hematology, clinical chemistry) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study medication administration even though it may have been present before the start of the study or those associated with underlying disease including expected progression, signs, or symptoms of the disease/disorder being studied.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- The disease/disorder being studied.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

The term 'life-threatening' in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to Sponsor/Sponsor's designee in lieu of completion of the Verona Pharma /AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by groups such as the Sponsor/Sponsor's designee, Health Authority, or Ethics Committee. In this case, all patient identifiers, with the exception of the subject/patient number, will be redacted on the copies of the medical records before submission to records to the Sponsor/Sponsor's designee.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.

- **Grade 1**: Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the subject's usual activities of daily living.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- **Grade 2**: Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- **Grade 3**: Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.
- **Grade 4**: Events that are potentially life threatening.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Chronicity

- Single occasion: Single event with limited duration.
- Intermittent: Several episodes of an event, each of limited duration
- Persistent: Event which remained indefinitely.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE. The AE must be characterized as unrelated, unlikely to be related, possibly related, probably related, or unknown (unable to judge).
    - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
    - "Possibly related" suggests that the association of the AE with the study medication is unknown; however, the AE is not reasonably supported by other conditions.
    - "Unlikely to be related" suggests that only a remote connection exists between the study medication and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
    - "Unrelated" is used if there is not a reasonable possibility that the study medication caused the AE.
    - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable (e.g., because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation).
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor/Sponsor's designee. However, it is very important that the Investigator always make an

assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/Sponsor's designee.

- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Action and Outcome

- Action taken with study medication (none, study medication stopped, study medication temporarily interrupted)
- Other actions (none, concomitant medication, study discontinuation, hospitalization, other)
- The outcome and date of outcome according to the following definitions:
  - Recovered or resolved (adverse event disappeared)
  - Recovered or resolving (patient is recovering)
  - Not recovered or not resolved (adverse event remains without signs of improvement)
  - Recovered or resolved with sequelae (adverse event has resulted in permanent disability or incapacity)
  - Fatal
  - Unknown (only applicable if patient has been lost to follow-up)
- Seriousness (yes or no)

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor/Sponsor's designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor/Sponsor's designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor/Sponsor's Designee within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the Sponsor/Sponsor's designee via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor/Sponsor's designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the study center will use the paper SAE data collection tool (see next section).
- The study center will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study center receives a report of a new SAE from a patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study center can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in Appendix 2 on the Medical Monitor Contact Information page.

SAE Reporting to Sponsor/ Sponsor's Designee via Paper CRF if eCRF is not available

- If the eCRF is not available, facsimile transmission of the SAE paper CRF may be used to transmit this information to the medical monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Appendix 2 in **Table 17**.

Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information for Patients

Contraception Guidance

Male Patients

- Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following from the first dose up to 30 days after the last dose of study medication:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition, male patients must refrain from donating sperm for the duration of the study and for 30 days after the last dose of study medication.
- Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study and for 30 days after the last dose of study medication.

Female patients

Female patients of childbearing potential are eligible to participate if they are not breastfeeding and agree to either abstinence or use at least one primary form of highly effective contraception not including hormonal contraception from the time of screening through Day 60.

Pregnancy Testing:

- WOCBP should only be included after a negative highly sensitive pregnancy test.
- Additional pregnancy testing should be performed at times specified in the SoA (Section 1.3).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Pregnancy testing will be performed and assayed in the central laboratory.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male subject is in the study. This applies only to male patients who receive ensifentrine.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and

submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Patients who become pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.6.5. While the Investigator is not obligated to actively seek this information in former patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study medication and be withdrawn from the study.

Appendix 6: Signature of Investigator

PROTOCOL TITLE: A SINGLE-CENTER PILOT RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ENSIFENTRINE IN THE RECOVERY OF HOSPITALIZED PATIENTS WITH COVID-19.

PROTOCOL NO: RPL554-COV-201

VERSION: 4.0

Version Date: 13 October 2020

This protocol is a confidential communication of Verona Pharma. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name title and the name of the study center in which the study will be conducted. Return the signed copy to the Sponsor.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator Date

Printed Name

Investigator Title

Name/Address of Center